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What Is the Role of Radiotherapy in Malignant Pleural Mesothelioma?

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ABSTRACT

Objective. **A review of the evidence supporting the use of radiotherapy in patients with mesothelioma was performed.**

Methods. **Relevant publications were searched for on Medline.**

Results. **In a Medline search on radiotherapy and mesothelioma, 611 hits were obtained. A limited number of prospective phase II trials of radiotherapy as part of trimodality protocols for early disease and in the palliation of pain were found, along with three small randomized controlled trials of port-site prophylaxis.**

Conclusion. **No randomized data exist to support the use of radiotherapy after radical surgery, although there are a large number of publications describing its use as an integral part of therapy, including seven phase II studies. One ongoing trial is randomizing patients to radiotherapy or not after extrapleural pneumonectomy. None of these studies provided any assessment of radiotherapy independent of the other modalities investigated, nor did any formally assess intensity-modulated radiotherapy. There have been several reports of excessive toxicity with this technique, and its use should be limited to phase I studies until the basis of this toxicity is better understood. Three trials have looked at port-site prophylaxis, one supporting its use and two showing no evidence of benefit. Two studies addressed pain control prospectively, one showing definite but short-lived benefits.**

Implications. **Radiotherapy is widely used in treating mesothelioma with little supporting evidence. More randomized trials are required to justify this use in all three common settings for its use.** ***The Oncologist*** 2011; 16:359–365

INTRODUCTION

Radiotherapy is widely used in the treatment of patients with mesothelioma, as an integral part of trimodality therapy for early stage disease, in the prophylaxis of port-site recurrence and in the palliation of pain. The purpose of this review is to identify the published evidence on which this practice is based, to identify gaps in the evidence which could be filled, and indicate those areas where current practice appears to fly in the face of existing published evidence.

METHODS

A Medline search using the terms radiotherapy and mesothelioma was performed, producing 611 hits. Those available in the English literature, and referring to clinical practice, were

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identified and form the basis of this review. No detailed analysis of the literature relating to technical aspects of radiotherapy has been attempted, although these issues will be alluded to when relevant. The review is divided into three sections referring to the different areas of practice described above.

RESULTS

Radiotherapy As a Component of Radical Treatment

Trimodality therapy with curative intent has been attempted, and described in small series, for over 30 years. An early report of eight patients treated with surgery, radiotherapy, and doxorubicin-containing chemotherapy found no patient relapse-free beyond 2 years [1]. At Memorial Sloan-Kettering, pleurectomy was supplemented with intrapleural implantation with I^{125} and P^{32} and adjuvant external beam radiotherapy to 45 Gy, but with 2-year disease-free survival of only 13% [2]. Radiological and clinical deterioration in lung function after high-dose radiotherapy was also reported at an early stage in these series. Maasilta [3] observed almost complete radiological opacification of the hemithorax a year after radiotherapy, with reduced lung volumes and diffusion capacity and hypoxia in one third of patients. These same authors observed no difference in outcomes to a range of radiotherapy schedules extending from 20 Gy in 10 daily fractions to 70 Gy in 56 fractions over 7 weeks. Only 2 of 57 patients were alive at 6 and 9 years [4].

Extrapleural Pneumonectomy and Adjuvant Radiotherapy

The era of widespread research interest in extrapleural pneumonectomy (EPP) for pleural mesothelioma was heralded by Sugarbaker et al.'s report [5] of 22% 5-year survival in 120 patients whose tumors were resected over a 15-year period. Postoperative radiotherapy was part of the protocol described and has remained so in almost all subsequent studies, although one of the best reported outcomes was in patients who did not receive radiotherapy [6]. No randomized data have been produced to support a role for adjuvant radiotherapy, but an increase in dose to 54 Gy in New York was associated with a reduction in local failure to 7 of 62 (11%) [7] compared to the 35% of 49 patients previously reported in Boston [8]. A subsequent report from Boston comparing 25 patients treated between 1994 and 2002 with 30 Gy to the hemithorax, 40 Gy to the mediastinum, and 54 Gy to original sites of disease with 14 patients treated in 2003 and 2004 to 54 Gy to the hemithorax found no dose effect [9].

Table 1. Published series of IMRT following EPP

Study	No. entered	No. alive and disease-free	Early nonmesothelioma mortality
MD Anderson [13]	63	8 @ 35 mo(s)	7
Brigham [15]	13	3 @16 mo(s)	6
Swedish C.I [16]	14	Not reported	0
Rigshospitalet [17]	26	Not reported	5
Miles [18]	13	6 @ 9 mo(s)	1

Abbreviations: EPP, extrapleural pneumonectomy; IMRT, intensity modulated radiotherapy.

Intensity Modulated Radiotherapy

Further attempts at improving local control with radiotherapy after EPP have focused on intensity modulated radiotherapy (IMRT), initially in the curative setting at MD Anderson [10, 11] and in the palliative setting in Heidelberg [12]. See Table 1. In the initial report of the former, local control at 13 months with minimal toxicity was reported in 7 patients; in the latter, median survival was 6.5 months from radiotherapy. The MD Anderson series was later updated to 63 irradiated patients of 100 who originally underwent EPP, the remainder having died (11), progressed (15), become unfit (9), or refused (2). In-field recurrence occurred in 3, locoregional failure in 8, but systemic failure in 33 [14]. However, early mortality was significant with 23 deaths within 6 months, including 10 from recurrence, 4 from pneumonia, 2 from pneumonitis, 2 from pulmonary embolism, and 1 from a bronchopleural fistula, with the volume of lung receiving 20 Gy or greater (V_{20}), predicting increased treatment-related mortality. These data reinforced the experience in Boston where 6 of 13 patients treated with IMRT died from radiation pneumonitis after receiving a prescribed dose of 54 Gy in 30 daily fractions with lung V_{20} <20% [15]. The authors suggested this was related to higher radiation doses in the single lung after extrapleural pneumonectomy, although the possibility of underlying undiagnosed asbestos-related interstitial lung disease was not explored. Other retrospective series have also reported outcomes with IMRT following EPP. Budduhan and colleagues [16] reported a 14% local recurrence rate in 14 patients treated with IMRT compared with 42% in 24 patients receiving conventional radiotherapy. They reported no treatment-related deaths with a prescribed dose of 50.4 Gy in 30 daily fractions and median lung V_{20} of 7%. Kristensen et al. [17] reported 4 deaths from radiation pneumonitis in 26 patients receiving chemotherapy, EPP, and IMRT with a prescribed dose of 50 Gy in 30 daily fractions and median lung V_{20} of 14%. The group who developed pneumonitis had a significantly higher mean volume of

Table 2. Prospective studies of trimodality therapy including extrapleural pneumonectomy

Study	No. entered	No. completing all therapy	Median survival [mo(s)]	Protocol-related deaths
Umberto I, Venice [25]	54	32	20	2
Memorial Sloan-Kettering, New York [26]	21	8	19	0
Padua [27]	21	15	25.5	0
SAKK [28]	61	36	19.8	1
Marmara, Istanbul [29]	20	12	16	1
U.S. multicenter [31]	77	40	16.8	3
EORTC [30]	59	37	18.3	5

lung receiving 10 Gy or greater (V_{10}), but there was a substantial overlap of individual values. Miles et al. [18] reported 13 patients treated between 2005 and 2007 at Duke University with IMRT to a median dose of 45 Gy after EPP. One patient died from radiation pneumonitis with a lung V_{20} of 7% and volume of lung receiving 5 Gy or greater (V_5) of 92%. Six patients had relapsed and 6 were alive and disease-free with median follow-up of 9.5 months.

Several planning studies have suggested IMRT reduced dose to organs at risk such as liver, heart, and kidneys [19] and lung [20], although the latter seemed to conflict with the clinical data. However, other studies suggested that conventional techniques gave lower doses to the contralateral lung, heart, and contralateral kidney, with little effect on target, ipsilateral kidney, spine, or liver [21, 22]. Moreover, it has been suggested that commercial planning systems might underestimate the dose in areas outside the target volume where the absorbed dose was less than half the prescribed dose [23]. Following the toxicities reported above, the Boston group has attempted to make their constraints for beam distribution and prescribed dose more rigorous, producing superior plans to those used previously but without any supporting clinical data yet to show reduced toxicity [24]. Currently, it must be concluded there is no evidence for benefit from IMRT after EPP, and its use must be considered experimental in carefully monitored phase I studies. The reasons why some patients are more sensitive to this form of treatment are unclear, and planning parameters do not clearly divide those at increased risk of death because of radiotherapy from those who are not at such risk.

Prospective Studies of Trimodality Therapy

No randomized data exist yet looking at post-EPP radiotherapy, although a Swiss trial is expected to reach completion in 2011. No formal prospective protocol (i.e., with a phase II design with specified hypothesis) has featured IMRT, but 7 prospective studies of trimodality therapy with conventional radiotherapy have been reported [25–31] involving 313 patients (Table 2). The Memorial Sloan-Kettering series [25] was in patients with inoperable stage III-IV disease, with a primary endpoint of 20% response to chemotherapy, which was achieved (26%). Three patients were alive and disease-free at time of report. The study reported by Krug et al. [31] was powered to find a 7% pathological complete response rate at EPP; this was not achieved, the rate in the intention-to-treat population being 4%. The EORTC trial [30] also failed to achieve its primary endpoint, the proportion of patients alive and disease-free and with residual toxicities grade 2 or less 3 months off protocol treatments. The target was 50%, but it was achieved in only 41%. The Swiss trial [28] was designed to find a 20% reduction in psychological distress between baseline and 3 months after surgery, which under normal circumstances would have been mid-radiotherapy. No change in rates of distress was seen. In all but one study, median survival was between 16 and 20 months, but almost half of patients failed to complete all planned therapies. A further study, of which the results have not yet been presented, has examined the feasibility of carrying out a phase III trial comparing trimodality therapy and chemotherapy alone. Of 112 patients who were thought operable at presentation and commenced chemotherapy, 50 were ultimately randomized to EPP plus radiotherapy or further nonsurgical management [32].

Current evidence suggests that a small group of patients thought operable, who are found at surgery to have early stage, node negative, epithelioid disease and achieve complete resection, have an expectation of prolonged survival, but because they cannot be identified preoperatively, a larger group of patients with very little chance of long-term survival must also undergo this aggressive treatment with its high morbidity and measurable mortality. Moreover, it remains unclear what chemotherapy or radiotherapy adds to the surgery, and what IMRT may add to the risks of treatment, again with no evidence that it produces any benefit.

Table 3. Randomized trials of port-site prophylaxis

Study	No. entered	Radiotherapy dose (Gy/fractions)	Port-site failure without radiotherapy (%)	Port-site failure with radiotherapy (%)
Marseille [38]	40	21/3	20	0
Perth [39]	58	10/1	10	7
Beatson [40]	56	21/3	12	13

Pleurectomy/Decortication and Adjuvant Radiotherapy

Disappointment at the relative failure of EPP has led many centers back to pleurectomy/decortication (P/D) plus adjuvant chemotherapy and radiotherapy. No data on quality of life changes consequent upon this therapy are available. A series of 123 patients treated at Memorial Sloan-Kettering between 1974 and 2003 reported 13-month median survival and only two protocol-related deaths [33]. In a series of 32 patients treated in San Francisco between 1995 and 2000, median survival was 18 months, although median follow-up was only 9 months [34]. In a phase II study of 49 patients receiving four-modality therapy including immunotherapy, median survival was 26 months [35]. Luckraz et al. [36] also reported 26-month median survival in 24 patients treated by P/D, chemotherapy, and radiotherapy, of 217 patients assessed. In this series this produced better outcomes than achieved in patients selected for EPP in the same center over the same period. It is to be hoped that future surgical studies will at least compare P/D with EPP, although many centers are likely to abandon EPP given the high mortality and morbidity and small number of long-term survivors. Any such studies should randomize the radiotherapy component rather than simply assume a benefit and include it automatically.

Radiotherapy for Port-Site Prophylaxis

The use of radiotherapy in this setting was first described in 20 patients who had 38 port-sites irradiated without any recurrences [37]. A subsequent French trial appeared to confirm this, with 0 of 20 recurrences in 20 treated sites after 21 Gy in 3 daily fractions and 8 recurrences in 20 unirradiated sites [38], but 2 more recent randomized trials [39, 40] found no benefit of radiotherapy, in the context of a much lower relapse rate in the range 10%–15% without radiotherapy, in line with other recent studies (Table 3) [41]. One of these studies could be criticized for its use of a single fraction of relatively low energy electrons which might have underdosed the pleural target in some patients. Only the last trial occurred in the era of routine chemotherapy with pemetrexed-based combinations. A survey in The Netherlands and Belgium [42] found that 32 of 38 (84%) of centers were sufficiently swayed by this evidence to offer prophylactic port-site radiotherapy, whereas in the United Kingdom 75% of centers used this treatment [43]. Occasional small retrospective series continue to be published [44, 45] but to date attempts to design randomized trials large enough to answer this question definitively have not been funded. Accordingly, many thousands of fractions of radiotherapy continue to be given annually with unconvincing supporting evidence, and despite the lack of any evidence that this is regarded by patients as a significant problem, and the likelihood that it is only one event in the general progression of the disease, with its prevention having no effect on the survival of patients or the natural history of the disease.

Radiotherapy for Palliation of Symptoms

Most publications in this area are retrospective descriptions of single center practice, with only two prospective trials. Gordon et al. [1] reported 29 courses in 19 patients, for dyspnea, dysphagia, superior vena cava obstruction, and brain metastases, with substantial palliation in 5 of 29 patients correlating with radiotherapy doses of >40 Gy. A series from Melbourne [46] reported that 65% of 26 courses of palliative radiotherapy were "at least partly successful." In a subsequent update they described some symptomatic relief in over half of patients without evidence of dose response [47]. The first prospective assessment of the role of radiotherapy in palliation was performed in Glasgow in the 1980s [48]. Twenty-two patients received 30 Gy in 10 fractions to the whole hemithorax for pain; 13 had less pain at 1 month, but this had fallen to 3 by 3 months and 1 by 5 months. Median survival was only 4 months. In a second study in Sweden [49], 47 patients received 40 Gy in 20 fractions to the hemithorax; 16 subsequently received doxorubicin and cyclophosphamide. Only 1 of 31 (3%) exhibited a partial response, and the authors reported no favorable effect on chest pain, weight loss, and performance status. Senan and colleagues reviewed the results of 227 radiotherapy courses in 189 patients during a 17-year period; response was slightly more common with fractions of 4 Gy or greater with a median time to recurrence of pain of 2 months [50].

Discussion

A previous review of radiotherapy in mesothlioma concluded "there is limited evidence for the role of radiotherapy in the management of patients with MPM. Future studies including radiotherapy for the treatment of such patients should include formal measures of quality of life and symptom control" [51]. Nothing has happened since that was written to alter the conclusion. Much work has gone into exploring methods of radical treatment in the few thought suitable for this treatment, again without any evidence that such treatment is of any value, and very little into the palliation of symptoms for what remains an incurable disease in all who present with it.

Extensive phase II data has shown little evidence of a treatment effect with trimodality therapy, and phase III trials may not follow, because the size of trial required to show an effect is likely to be prohibitive. Most phase II studies suggest a very small cohort of long-term survivors, but this may be a reflection of indolent biology rather than efficacy of treatment, and no predictive factor that identifies these patients has yet been found. Attempts at improving the results of radiotherapy by increasing treatment complexity have if anything had the reverse effect. The available evidence suggests IMRT should not be used after EPP except under strict trial protocols, and even then as a phase I procedure to establish what the safe levels of dose are to contralateral lung and other organs at risk. It may become clearer in 2011 when the ongoing SAKK trial is analyzed whether radiotherapy has any role after EPP, but if phase III trials are opened to examine the value of EPP, further questions regarding the role of adjuvant therapy should be included, with some patients randomized to no radiotherapy (and no chemotherapy). It is likely that some centers will continue to offer chemotherapy, EPP and radiotherapy as a treatment package and it is to be hoped that they will enroll their patients in biological studies to investigate predictive factors.

The role of radiotherapy after P/D is equally unclear. Because this is by definition a palliative procedure, quality of life data are urgently needed to justify the continued enthusiasm for it, and any radiotherapy included in P/D protocols should be subject to randomization. In the meantime, there does not seem to be any justification for radiotherapy outside such protocols given the lack of any evidence of benefit and the significant possibility of harm.

As with early stage disease, the available evidence does not support a role for radiotherapy in port-site prophylaxis, and its role should be regarded as experimental. Whether the frequency of port-site recurrences and the symptoms that they cause justify adjuvant therapy is itself a matter for debate, but if its use is to continue, rather than simply be abandoned as a waste of time, it should be subjected to randomized trials that include quality of life and economic endpoints.

Perhaps the most promising role for radiotherapy is in the palliation of pain. In patients with end-stage disease with pain resistant to opiates, steroids, anticonvulsants, anaesthetic agents, and nonsteroidal anti-inflammatory agents, palliative radiotherapy may improve pain control, with the duration of pain control indicated by the available data sufficient to last most of the remaining life of these patients. The very wide fields required may cause significant fatigue, and again if a role is thought to exist for radiotherapy in this setting, prospective studies showing improved pain control and tolerable side effects are required. The applicability of the available prospective data to the modern era of aggressive palliative medicine is questionable, but the data do suggest a potential role that warrants investigation.

Summary

There is currently no evidence to support the routine role of radiotherapy in patients with mesothelioma. Its role in early stage disease as a surgical adjuvant will depend on the prevailing surgical fashion, but evidence of efficacy after either EPP or P/D is required if it is to remain part of ongoing protocols. Its role in port-site prophylaxis has been cast into doubt by recent randomized trials, and this use should be discontinued until evidence of benefit is shown in larger trials in the chemotherapy era. There may be a role in the management of poorly controlled pain, but again prospective evidence of benefit with modern treatments should be sought.

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